

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 June 2001 (27.06.01)	
International application No. PCT/US00/26241	Applicant's or agent's file reference X-13199
International filing date (day/month/year) 06 October 2000 (06.10.00)	Priority date (day/month/year) 20 October 1999 (20.10.99)
Applicant BUMOL, Thomas, Frank et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

24 April 2001 (24.04.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number
WO 01/28582 A2

- (51) International Patent Classification⁷: A61K 38/17, A61P 11/00
- (21) International Application Number: PCT/US00/26241
- (22) International Filing Date: 6 October 2000 (06.10.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/160,613 20 October 1999 (20.10.1999) US
- (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): BUMOL, Thomas, Frank [US/US]; 12006 Eden Glen Drive, Carmel, IN 46033 (US). COHEN, Fredric, Jay [US/US]; 15 Autumn Drive, Newtown, PA 18940 (US).
- (74) Agents: WEBSTER, Thomas, D. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTIC APPLICATIONS OF FLINT POLYPEPTIDES

(57) Abstract: FLINT protein is useful as a medicament in treating and/or inhibiting lung disorders and in inhibiting T cell proliferation. Therapeutic compositions and methods of treatment utilizing FLINT are provided.



WO 01/28582 A2

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

WEBSTER, Thomas D. et al
ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis Indiana 46285
ETATS-UNIS D'AMERIQUE

Received
MAR 11 2002
Eli Lilly and Company
Patent Division

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 21.02.2002

Applicant's or agent's file reference
X-13199

IMPORTANT NOTIFICATION

International application No.
PCT/US00/26241

International filing date (day/month/year)
06/10/2000

Priority date (day/month/year)
20/10/1999

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

 European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Exner, K

Tel. +49 89 2399-7826




PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-13199	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/26241	International filing date (day/month/year) 06/10/2000	Priority date (day/month/year) 20/10/1999
International Patent Classification (IPC) or national classification and IPC A61K38/17		
Applicant ELI LILLY AND COMPANY et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 		
Date of submission of the demand 24/04/2001	Date of completion of this report 21.02.2002	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pa I Soto, R Telephone No. +49 89 2399 7346	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/26241

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, pages:

1-28 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/26241

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 8-12 (industrial applicability).

because:

- ☒ the said international application, or the said claims Nos. 8-12 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 2, 3, 5-12
	No: Claims 1, 4
Inventive step (IS)	Yes: Claims
	No: Claims 1-12
Industrial applicability (IA)	Yes: Claims 1-12 (see separate sheet)

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/26241

No: Claims

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/26241

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- 1.1. **Claims 8-12** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 2.1. The present application relates to:

- (i) **FLINT** for use in the treatment and/or inhibition of a lung disease (**claim 1**),
- (ii) the use of **FLINT** in the manufacture of a medicament for the treatment and/or inhibition of a lung disease (**claim 4**),
- (iii) the use of **FLINT** to manufacture a medicament for inhibiting T cell activation (**claim 6**), and
- (iv) a method for treating or inhibiting pulmonary fibrosis (**claims 8 and 9**), for treating or inhibiting chronic obstructive pulmonary disease (**claims 10 and 11**), and for inhibiting T cell activation (**claim 12**) comprising administering to a patient in need thereof an effective amount of **FLINT**.

- 3.1. The present application does not satisfy the requirements of the PCT with respect to novelty (Art. 33(2)) for the following reasons.

D1 (see the passages cited in the Search Report) discloses that **FLINT** inhibits both **FasL** apoptosis-inducing activity and proinflammatory activity. The use of **FLINT** for the treatment of disorders associated with apoptosis and inflammation is also disclosed, and some of the cited disorders concern the lung: lung cancer, pneumonia, and acute respiratory distress syndrome **ARDS**. This is **novelty destroying** for present claims **1 and 4**.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/26241

- 3.2. Present claims 2-3 and 5-12 appear to be novel over the prior art.
- 4.1. However, present claims 2-3 and 5-12 do not involve an inventive step (Art. 33(3) PCT) for the following reasons.
- 4.2. **D1**, which is regarded as the closest prior art, discloses that FLINT inhibits FasL apoptosis-inducing activity and proinflammatory activity, and LIGHT mediated-activity. The use of FLINT for the treatment of disorders associated with apoptosis and inflammation including lung disorders is also disclosed. The present application, according to claims 2-3 and 5-12, differs from **D1** in that FLINT is used to treat or prevent some specific lung diseases, i.e. pulmonary fibrosis and chronic obstructive pulmonary disease. Thus, the **problem** to be solved by the present application is regarded in the finding of specific lung disorders which can be treated with FLINT.
- 4.3. The **solution** provided by the present application according to claims 2, 5 and 8-9, i. e. the treatment or inhibition of pulmonary fibrosis is rendered obvious by **D1** in combination with **D2**. **D2** (see the passages cited in the International Search Report) discloses that pulmonary fibrosis is characterised in abnormal apoptosis induced by FasL-Fas pathway and inflammation and that the inhibition of FasL-Fas pathway prevents pulmonary fibrosis. It further suggests the use of FasL-Fas pathway inhibitors for the prevention of pulmonary fibrosis. The teaching of **D2** would certainly prompt the skilled person to use FLINT for the treatment of pulmonary fibrosis. Accordingly, **no inventive step is recognised in the subject-matter of present claims 2, 5 and 8-9.**
- 4.4. The **solution according to present claims 3, 7 and 10-11**, i.e. the use of FLINT for treating chronic obstructive pulmonary disease, is also obvious in the light of the prior art. COPD (see lines 1-5 on page 10 of the present application) has already been associated with an increased Fas-induced apoptosis. This would also prompt the skilled person to use FLINT, which is known from **D1** to be an inhibitor of Fas, for treating or inhibiting COPD. Accordingly, **no inventive step is recognised in present claims 3, 7 and 10-11.**
- 4.5. The **solution according to present claims 6 and 12**, i.e. the use of FLINT for inhibiting T cell activation, is also rendered obvious by **D1**, in this case in combination

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/26241

with **D3**. **D1** discloses that FLINT inhibits LIGHT. On the other hand, **D3** (see the passages cited in the search report) discloses that HVEM-L (LIGHT) stimulates T cell proliferation. Thus, it would be obvious to the skilled person that FLINT is also useful for inhibiting T cell activation.

- 5.1. For the assessment of the present claims 1-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X-13199	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 26241	International filing date (day/month/year) 06/10/2000	(Earliest) Priority Date (day/month/year) 20/10/1999
Applicant ELI LILLY AND COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/26241

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/17 A61P1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 50413 A (MIZRAHI JACQUES ;HEUER JOSEF GEORG (US); NOBLITT TIMOTHY WAYNE (US) 7 October 1999 (1999-10-07)	1,4
Y	page 10, line 26 -page 11, line 18 page 12, line 11 - line 22 page 14, line 20 -page 15, line 29 page 21, line 3 - line 26 page 31, line 16 - line 18 page 32, line 6 - line 11 page 33, line 28 -page 34, line 1 claims 5,7,15,37,39,47,64,66,74 --- -/--	2,5,6,8, 9,12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *I* earlier document but published on or after the international filing date
- *I* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

24 April 2001

Date of mailing of the international search report

11/05/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stein, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/26241

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KUWANO KAZUYOSHI ET AL: "Essential roles of the Fas-Fas ligand pathway in the development of pulmonary fibrosis." JOURNAL OF CLINICAL INVESTIGATION, vol. 104, no. 1, July 1999 (1999-07), pages 13-19, XP002165816 ISSN: 0021-9738 cited in the application the whole document	2,5,8,9
Y	HARROP J A ET AL: "Herpesvirus entry mediator ligand (HVEM-L), a novel ligand for (HVEM/TR2, stimulates proliferation of T cells and inhibits HT29 cell growth" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 273, no. 42, 16 October 1998 (1998-10-16), pages 27548-27556, XP002109996 ISSN: 0021-9258 the whole document, especially page 27554 right handed column lines 34-37	6,12
P,X	WO 00 58466 A (MICANOVIC RADMILA ;LILLY CO ELI (US); RATHNACHALAM RADHAKRISHNAN () 5 October 2000 (2000-10-05) page 11, line 3 - line 18 page 22, line 9 - line 15 page 46, line 24 -page 49, line 14 claims 16-18,26; example 15	1-12
P,X	WO 00 58465 A (BECKER GERALD WAYNE ;COHEN FREDRIC JAY (US); GONZALEZ DEWHITT PATR) 5 October 2000 (2000-10-05) page 11, line 17 -page 12, line 16 page 14, line 29 -page 15, line 3 page 61, line 26 -page 64, line 11 claims 44,47-50	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/26241

Patent document cited in search report		Application date	Patent family member(s)		Publication date
WO 9950413	A	07-10-1999	AU 3369199	A	18-10-1999
			BR 9909328	A	12-12-2000
			NO 20004873	A	24-11-2000
			AU 2211100	A	12-07-2000
			WO 0037094	A	29-06-2000
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WO 0058466	A	05-10-2000	AU 3739400	A	16-10-2000
			AU 3739500	A	16-10-2000
			WO 0058465	A	05-10-2000
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WO 0058465	A	05-10-2000	AU 3739400	A	16-10-2000
			AU 3739500	A	16-10-2000
			WO 0058466	A	05-10-2000
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